REMARKS

Claim 1 has been amended. Claims 14-37 have been canceled as being drawn to a nonelected invention. New Claims 38-41 have been added.

Claims 1-13, and 38-41 remain in the application.

Claim 1 has been clarified to incorporate the definition of "three-dimensional" used in the specification. No change in the scope of the Claim is intended. Support for this amendment is found, for example, in the specification at page 28, line 22 through page 29, line 10.

Support for new Claim 38 is found, for example, in the specification at page 1, lines 16-20; page 3, lines 17-22; page 4, lines 8-10; and page 18, line 25 through page 19, line 3.

Support for new Claim 39 is found, for example, in the specification at page 1, lines 17-19; page 4, lines 23-25; and page 18, line 25 through page 19, line 3.

Support for new Claim 40 is found, for example, in the specification at page 19, lines 13-26; and page 21, line 26 through page 22, line 4.

Support for new Claim 41 is found, for example, in the specification at page 19, lines 16-17; and page 22, lines 1-3.

Enclosed is a check for the $750 fee for a request for continued examination (37 C.F.R. § 1.17(e)). If this amount is incorrect, please refer to the Deposit Account Authorization previously filed for this application. If any extension of time is required, please consider this paper a petition for the total extension of time required.

Reexamination and reconsideration of the application, as amended, are respectfully requested.

The Restriction Requirement

In view of the Office's November 19, 2002 clarification that Group II indeed includes each of Claims 14-23, 25, and 27-37, Claims 14-37 have now been cancelled as being drawn to nonelected inventions.

The election of Group I, Claims 1-13, without traverse is confirmed. Each of new Claims 38-41 corresponds to elected Group I.

The § 112, Second Paragraph Rejections

Claims 1-13 were rejected under 35 U.S.C. § 112, second paragraph on several grounds. The Office gave specific grounds of rejection only for Claims 1 and 2, so it is assumed that the remaining Claims were rejected solely due to their dependence from independent Claim 1.

Claim 1

Claim 1 was said to be indefinite in the phrase "if any." Some tissue samples will exhibit angiogenesis, while other tissue samples will exhibit no angiogenesis. In the latter case, no angiogenic vessels will be observed. An observation that there is no angiogenesis associated with a particular sample can provide useful and valuable information. Therefore it is appropriate and accurate for the Claim to refer to "angiogenic vessels, if any."

The Office also said that "the claim does not indicate what is a 'time sufficient' to incubate and to observe the tissue in order to demonstrate the fact that there is no growth of angiogenic vessels . . . ." It is respectfully submitted that not only is the limitation in question definite, but that it highlights the need for the phrase "if any" to which the Office also objected. The full limitation in question is incubating "for a time sufficient to allow angiogenic vessels, if any, to grow into the matrix . . . ." A person of ordinary skill in the art would readily understand this limitation to mean that the time is sufficient for angiogenic

vessels to grow into the matrix -- assuming that there are angiogenic vessels -- and otherwise, that the time is sufficient to demonstrate the fact that there are none, because angiogenic vessels would have grown into the matrix within the allotted "sufficient" time, had such vessels been present.

The Office's attention is respectfully directed to M.P.E.P. § 2173.05(g), "Functional Limitations": "A functional limitation is an attempt to define something by what it does, rather than by what it is . . . . There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. . . . A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient, or step." (citations omitted)

The Office inquired whether the time would be a day, a month, or a year. In general, an adequate time would typically be on the order of a few days to a few weeks, but a worker of skill in the art could readily alter the culture conditions to facilitate faster or slower growth. Biological inventions are frequently not susceptible of definition with mathematical precision. In the present case, a person of ordinary skill in the art could readily determine an appropriate time by, for example, growing one or more comparable samples with known angiogenic properties as control(s), under otherwise identical conditions, to determine what a suitable time is for such conditions. A person of ordinary skill in the art, given the teachings of the present specification, could readily determine and understand what

constitutes "a time sufficient to allow angiogenic vessels, if any, to grow into the matrix . . ." for a particular set of conditions.

Functional language is permissible, and in many instances is a preferred manner to define an invention. The use of functional language in Claim 1 introduces no indefiniteness; a person of ordinary skill in the art would readily understand the claim limitations as currently written. It is respectfully submitted that this ground of rejection should be withdrawn.

Claim 2

Claim 2 was said to be indefinite in its use of the word "substantially." The Office has recognized that the M.P.E.P. acknowledges that the use of the term "substantially" is often definite, depending on context. See M.P.E.P. § 2173.05(b), subheading D. The Office asserted, however, that the term was nevertheless indefinite because neither the specification nor the Claims gave particular definitions of amounts that were included or excluded by the term "substantially."

It is respectfully submitted that the Office is mistaken in asserting that the term "substantially" must find specific metes and bounds in the specification or in the claims before the term may be considered definite. M.P.E.P. § 2173.05(b), subheading D gives two examples in which the term substantially has been found by the Courts to be definite: in one example, the specification did provide general guidelines; but in the second example, the Court found the term definite because "one of ordinary skill in the art would know what was meant by 'substantially equal.'" (citations omitted)

In the context of Claim 2, the term "substantially" is definite. A person of ordinary skill in the art would readily understand the meaning of the term in context, and § 112, second paragraph is therefore satisfied. There is no requirement for mathematically precise metes and bounds if, as in the present case, a person or ordinary skill in the art would readily understand the meaning of the limitation in question.

The full expression appearing in Claim 2 is "wherein the medium contains substantially no exogenous angiogenesis-enhancing factors and substantially no exogenous angiogenesis-suppressing factors." In other words, it is not necessary to exclude every last molecule of any enhancing or suppressing factors. The limitation is, of course, consistent with the complete absence of enhancing or suppressing factors. But a person of ordinary skill in the art would readily understand that the limitation is also consistent with the possible presence of small quantities of enhancing factors, or small quantities of suppressing factors, or both. However, if such a factor is present, then its concentration should be such that the observed angiogenesis of tissue samples in the medium is substantially the same, on average, as would be observed in an otherwise identical medium that completely lacked the factor. If the observed average angiogenesis were substantially different from that in an otherwise identical medium that completely lacked the factor, then the medium would not be considered to be substantially free of the factor. A person of ordinary skill in the art would readily comprehend the meaning of these limitations. The Claim limitations in question are definite.

§ 112, Second Paragraph Summary

It is respectfully submitted that all § 112, second paragraph rejections have been overcome or should be withdrawn.

The §§ 102 and 103 Rejections

All Claims were rejected under 35 U.S.C. §§ 102(b) and 103 as being both anticipated by, and obvious over, one or more of four different references cited by the Office.

It is respectfully submitted that the claimed inventions are both novel and nonobvious over the cited references, whether those references are considered individually or in combination.

Claim 1 is the sole independent Claim within this Group of Claims. Without waiving the right to assert alternative arguments in the future, in the interest of brevity Applicants will discuss only Claim 1 for the time being. If independent Claim 1 is novel and nonobvious, then it logically follows that dependent Claims 2-13 must also be novel and nonobvious. Further in the interest of brevity, for the time being only a single reason will be argued why Claim 1 is distinguishable from the cited references, since that reason is particularly straightforward.

Essentially the same reason was argued in response to the previous office action -- namely, that none of the cited references taught or suggested the limitation of "embedding a three-dimensional mammalian tissue sample in a matrix," where "three-dimensional" has the specific definition given in the present specification. If the undersigned understands the Office's November 19, 2002 remarks correctly, it appears that the Office had no

disagreement with the substance of the Applicants' position. Rather, the Office's position appears to be that the Applicants had improperly attempted to read limitations from the specification into the Claims in order to distinguish the cited references.

Applicants respectfully disagree with the Office's position. It is well settled that a patentee is entitled to be his own lexicographer. Nevertheless, in the interest of accelerating prosecution, the present amendment has expressly incorporated the specific definition of "three-dimensional" from the specification into Claim 1, thereby overcoming this ground of rejection. It is repeated that this amendment is intended as a clarification only. The amendment merely inserts into Claim 1 the definition of the term "three-dimensional" that was already clearly and expressly set forth in the specification.

The "three-dimensional tissue sample" limitation

Independent Claim 1 contains the following limitation that is neither taught nor suggested by any of the cited references:

> "embedding a three-dimensional mammalian tissue sample in a matrix"

The present amendment clarifies what this limitation means, by expressly adding the following definition to Claim 1:

> "wherein the three-dimensional tissue sample comprises multiple layers of cells comprising blood vessels and other cells of the tissue; and wherein the

architecture of the tissue sample, including blood vessels, supportive stromal elements, neural cells, and endothelial cells, is substantially intact and has not been disrupted as compared to that of comparable tissue *in vivo*"

Some of the advantages of the novel system over the prior references are explained in the specification at page 15, lines 1-20, and page 21, lines 1 through 24:

> No prior reports are known of angiogenesis assays for tumors or other tissue in which the intact three-dimensional structure of the tissue is maintained during the assay -- as opposed to, for example, reports of an assay conducted on an isolated artery or vein. . . .
>
> We have discovered an *in vitro* tissue angiogenesis and vasculogenesis system that allows the outgrowth of microvessels from a three-dimensional tissue fragment implanted in a matrix. . . . This system, which may be used with human or other mammalian or animal tissues, may be used in assaying tumor angiogenic potential . . . . The angiogenic potential of a tissue can be determined by measuring the growth of microvessels into the matrix. The system is based on endogenous angiogenesis, vasculogenesis, neovascularization, or tissue perfusion, independent of tumor angiogenesis or other tissue angiogenesis. By contrast, tumor angiogenesis *per se* results from the formation of patterned

networks of interconnected loops of extracellular matrix through which tumor perfusion may occur. The three-dimensional structure of the tumor or other tissue is maintained in the matrix, including its blood vessels, supportive stromal elements such as fibroblasts, and neural and endothelial cells. . . .

The invention allows a tumor or other tissue to induce an angiogenic response while maintaining an intact three-dimensional architecture.

The present invention offers several advantages. It allows the evaluation of a tumor or other tissue's angiogenic response while maintaining an intact three-dimensional architecture. Tumor (or other tissue) compartments may be evaluated simultaneously or separately. The novel system allows the evaluation of drugs that require activation *in vivo* and drugs that are active *ex vivo*. One advantage of this invention is that it may be used to provide a functional (as opposed to histological) angiogenic index. A functional angiogenic index may help to reveal tumors with a poor prognosis due to a high functional angiogenic index, even though they may have a low histological angiogenic index. A disparity between functional and histological angiogenic indices may occur if circulating anti-angiogenic substances (such as angiostatin/endostatin) mask the angiogenic potential of a tumor. . . .

The invention may also be used to develop prognostic tests for a patient's resistance or susceptibility to the future development of malignancy or angiogenesis-related diseases.

With this background, a straightforward examination of the cited references readily reveals that none of them teaches or suggests the use of a "three-dimensional" tissue sample within the scope of the definition of Claim 1.

U.S. Patent 5,856,184

The Office cited Col. 11, lines 15-40 of this patent. Col. 11, lines 16-20 of the '184 Patent describe the specimen used in the experiment: the thoracic aorta of a mouse was excised, fat was dissected away, and the aorta was sectioned into 1 mm segments. As amended, Claim 1 specifically states that "the three-dimensional tissue sample does not consist of an isolated artery or an isolated vein." Furthermore, the architecture of the tissue sample in the '184 patent was not kept substantially intact, as required by amended Claim 1. To the contrary, other tissue was dissected away from the aorta, leaving only an isolated artery; and the isolated aorta itself was then cut into 1 mm segments.

Brown

The Office cited the abstract and page 551, col. 1, lines 4-20 of Brown. The source of the vessel fragments discussed on page 551 is given on page 550, col. 1, under the heading "Preparation of blood vessel fragments." Superficial blood vessels were excised from the surface of human placentas, cut into 1- to 2-mm fragments, and freed of residual

clots. For the reasons just discussed, fragments of an isolated blood vessel are outside the definition found in Claim 1.

Montesano

The Office cited the abstract, page 807 (it is assumed that "page 870" was intended) at the "Materials and Methods" section, and figures 1 and 2. Montesano's abstract does include the words "three-dimensional." However, there is no indication of any sort that Montesano had the present definition of "three-dimensional" in mind. Furthermore, Montesano's reference to a particular "three-dimensional" element was in fact a reference to a three-dimensional matrix, not a three-dimensional tissue sample. See the first two lines of Montesano's abstract. The samples used were described in the first paragraph of the "Materials and Methods" section on page 870. Tissues (from various sources) "were minced into small fragments in a drop" of saline. One may therefore reasonably infer that the individual tissue fragments must have been considerably smaller than the size of a drop of saline. In the following paragraph, there is a further indication of the size of the "small fragments" where it is stated that the "tissue fragments were . . . allowed to sediment, and resuspended" in solution. The fragments must indeed have been small if it was necessary to allow them to sediment, and if they could be said to later be "resuspended." As stated in the examples following the detailed Definition found in the present specification, isolated cells from a disrupted tissue are not "three-dimensional" within the scope of the definition of Claim 1; nor is an agglomeration of such cells grown in culture -- even if the agglomeration has substantial thickness. See the present specification at page 29, lines 5-10.

The Office's November 19, 2002 remarks suggest that a point of clarification may be helpful. The Office's remarks suggest that the Office may have construed the Applicants' definition or the Applicants' earlier remarks to the effect that "three-dimensional" is based primarily upon some minimum size. To the contrary, the definition in Claim 1 requires that the architecture of the tissue sample be substantially intact, and not be disrupted as compared to that of comparable tissue *in vivo*. There is no minimum size *per se*. Rather, the disruption and suspension of cells described by Montesano leads one to the reasonable deduction that the size of the samples must necessarily have been so small that they could not have maintained any intact architecture. The definition of Claim 1 refers to a substantially intact tissue architecture. When a sample has been disrupted to a sufficiently small size, as was done in Montesano, then it will be a necessary consequence that the tissue architecture must have been disrupted in the process. Conversely, if the cells are then allowed to grow into an agglomeration in culture, even if that agglomeration becomes relatively thick, the agglomeration would not satisfy the definition of Claim 1. See the present specification at page 29, lines 5-10.

Lugassy

The Office has not cited any particular portion of Lugassy. Although this omission was pointed out in the August 26, 2002 Amendment, the November 19, 2002 Office Action still did not cite any particular portion of this reference. For the reasons given below, it is respectfully submitted that this ground of rejection should be withdrawn. Strictly in the alternative, the Office is respectfully requested to specify the portion(s) of Lugassy on which the Office has relied. See M.P.E.P. § 706.02(j), first paragraph: "After indicating that

the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office action: (A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate . . . ."

To date, Applicants have not obtained a translation of this reference. For the time being, therefore, these remarks are based the "Abridged English Version" on pp. 37-38. This reference does mention a "three-dimensional" element, but again, there is no indication that Lugassy taught or suggested the use of a "three-dimensional" tissue sample having "multiple layers of cells comprising blood vessels and other cells of the tissue; and wherein the architecture of the tissue sample, including blood vessels, supportive stromal elements, neural cells, and endothelial cells, is substantially intact and has not been disrupted as compared to that of comparable tissue *in vivo*."

To the contrary, the manner in which Lugassy's tumor model was prepared shows clearly that it was not a "three-dimensional" tissue sample satisfying the limitations of Claim 1. Lugassy teaches away from the present invention. Rather than use a "three-dimensional" tissue sample with substantially intact architecture, Lugassy teaches the use of a "rebuilt" tumor model, in which cells from a lymphoma cell line were mixed with angioma fibroblasts obtained by culturing explants from a human vascular angioma. The mixed cells were suspended in a collagen gel, which then grew into the "rebuilt" cancer. Cells from the "rebuilt" cancer became confluent in 4-8 weeks. This last statement implies that the cells were not confluent at an earlier time, i.e., that they were separated from one another. As previously discussed, isolated cells do not have the substantially intact architecture required by the limitations of Claim 1, nor does an agglomeration of such cells

grown in culture -- even if the agglomeration grows to substantial thickness. See the present specification at page 29, lines 5-10.

§§ 102 and 103 Summary

It is respectfully submitted that all prior art rejections should be withdrawn.

Compliance with 37 C.F.R. § 1.111(b) Regarding § 103 Rejections

The first paragraph on (unnumbered) page 13 of the November 19, 2002 Office Action is not understood: "With regard to the claim rejection under 35 USC § 103 applicants' arguments (page 11, par. 2) fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references."

The one-sentence paragraph to which the Office referred read simply "It is respectfully submitted that all prior art rejections should be withdrawn." The heading that immediately precedes this paragraph, "§102 and 103 Summary," clearly shows that the paragraph was intended only as a brief summary of the previous, detailed arguments concerning the prior art rejections. The August 26, 2002 Amendment discussed the § 102 rejections and the § 103 rejections together, as does the present amendment. If the Office interpreted the remarks on page 11, par. 2 of the prior amendment as being applicants' sole response to the § 103 rejection, then the applicants respectfully clarify that all discussions of the prior references are intended to address both the § 102 rejections and the § 103 rejection. The single-sentence summary appearing on page 11 was never

intended as a substantive reply to the prior art rejections, but only as a summary of the discussion that appeared in one section of the Amendment (concerning prior art rejections) before commencing the discussion in the next section (concerning the Information Disclosure Citation). For the reasons given above in detail, none of the references teaches or suggests the claimed inventions, whether the references are considered alone or in combination. Nothing in any of the cited references teaches or suggests the use of a three-dimensional sample having the limitations recited in Claim 1.

The Information Disclosure Citations

The August 9, 2002 Office Action enclosed a copy of the May 25, 2001 Information Disclosure Citation (PTO-1449) in which three of the four citations were stricken. An additional Information Disclosure Citation was therefore filed on August 26, 2002, supplying additional copies of the three stricken citations.

The November 19, 2002 Office Action stated that the August 26, 2002 information disclosure citation "fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered."

All cited references are in the English language. Therefore, 37 C.F.R. § 1.98(a)(3) is inapplicable. Subsection § 1.98(a)(3) requires an explanation of relevance only for references that are not in English. See M.P.E.P. § 609, part III, subpart (A)(3), second paragraph: "The requirement for a concise explanation of relevance is limited to

information that is not in the English language." The reason that was given by the Office for refusing to consider the references is therefore improper. In fact, an explanation for the citation of these references does appear in the specification, namely, at page 29, lines 12-23. They were cited both from an abundance of caution, and to provide a valid basis to support an incorporation by reference -- in case, with the benefit of hindsight, it later appeared that anything significant might otherwise have been inadvertently omitted from the specification.

The Office's attention is also respectfully directed to 37 C.F.R. § 1.97(h), which clearly contemplates the possibility that references cited in an Information Disclosure Statement might not be prior art to the application in which they are cited. A conclusion that a reference is not prior art is not a sufficient justification for striking it from an Information Disclosure Citation. If the Office concludes that these references are not prior art, then the proper procedure would be to initial the Information Disclosure Citation, but to refrain from basing any rejections on those references. See also M.P.E.P. § 609, paragraph 6: "Once the minimum requirements of 37 CFR 1.97 and 1.98 are met, the examiner has an obligation to consider the information."

The Office asserted that the two Gulec *et al.* papers were not publicly available documents. To the contrary, copies of both of these papers were submitted with the application as originally filed on May 25, 2001, and as a matter of fact are available to the public as part of the file wrapper of the present application. Furthermore, as a matter of law, neither 37 C.F.R. § 1.97 nor § 1.98 requires that a cited document be publicly available. To the contrary, 37 C.F.R. § 1.98(a)(1) refers to "patents, publications, applications, or other information." "Other information" must be something that is not a

publication, or the reference to "other information" would be superfluous. See also 37 C.F.R. § 1.98(2)(ii), which requires a legible copy of each publication, and § 1.98 (2)(iv), which requires a legible copy of "[a]ll other information." By contrast, 37 C.F.R. § 1.99, which governs third-party submissions in published applications, allows third parties to submit copies of "patents or publications" in § 1.99(a), while § 1.99(d) expressly prohibits third-party submission of "other information." Thus the Rules of the PTO clearly contemplate that patent applicants may submit "other information" that is neither a patent, nor a publication, nor an application; while third parties are limited to submitting patents and publications only.

The Office noted that the earlier-cited Coy *et al.* patent application has now issued as a patent. Applicants have accordingly cited the issued Coy *et al.* 6,465,613 patent on the enclosed new Information Disclosure Citation. For the record, Applicants note that this patent only issued very recently, on October 15, 2002, after the earlier Information Disclosure Citations had been submitted. It would not have been possible for the earlier Information Disclosure Citations to have cited Coy *et al.* by referring to an issued patent number, as none existed at the time. Applicants further note that the pertinence of this particular disclosure is discussed in the present specification at page 23, lines 11-18.

In addition to the Coy *et al.* patent, two new references are also cited in the enclosed new Information Disclosure Citation:

(1) The first newly-cited reference is S. Gulec *et al.*, "Antitumor and Antiangiogenic Effects of Somatostatin Receptor-Targeted *in Situ* Radiation with ^{111}In-DTPA-JIC 2DL," *J. Surg. Res.*, vol. 97, pp. 313-137 (2001). Applicants note that the material

in this paper was presented at the annual meeting of the Association for Academic Surgery, Tampa, Florida, November 2-4, 2000. This paper describes an *in vitro* human tumor angiogenesis model that is based on the implantation of fresh tumor fragments in a fibrin matrix that maintained the three-dimensional tumor architecture and that contained supportive stromal elements such as fibroblasts and neural and endothelial tissues.

(2) The second newly-cited reference is Parish *et al.*, U.S. Patent 5,976,782. This patent discloses methods for determining angiogenesis by culturing a blood vessel fragment in a physiological gel, such as fibrin, collagen, or Matrigel. This patent taught that "[p]referably, the blood vessel fragments are freshly isolated." Col. 3, lines 57-58. The working examples (e.g., Col. 7, lines 44-57) describe the preparation of what appear to be isolated blood vessel fragments, cut into 1-2 mm fragments with fine dissecting forceps and iridectomy scissors, and freed of residual clots. There was no suggestion that any cell layers were retained, other than those of the blood vessel fragments themselves. See also Col. 8, lines 40-48, which describes occasional contamination of cultures by fibroblasts, ways to inhibit fibroblast outgrowth, and the observation that the fibroblasts appeared only as a monolayer on the bottom of culture wells, unable to penetrate the fibrin gels. The patent also suggests testing extracts from tumors (e.g., extracts obtained by freeze-thawing tumor samples) in the isolated blood vessel assay to determine whether the extracts are angiogenic. See Col. 11, lines 27-38.

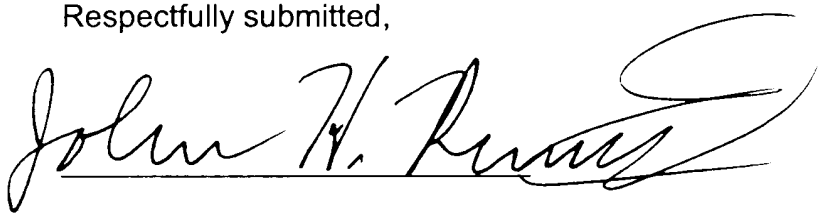
The Applicants have fulfilled the requirements of 37 C.F.R. §§ 1.97 and 1.98 with respect to each of the references cited in both the enclosed Information Disclosure Citation, and the August 26, 2002 Information Disclosure Citation, and are entitled to have them considered by the Office. The Office is respectfully requested to consider all references cited in both Information Disclosure Statements, and to return copies of the Information Disclosure Statements with the next communication concerning this application. If the Office concludes that the cited references are not prior art, or otherwise do not form a basis for rejecting any of the claimed inventions, then the Office need do nothing further, beyond acknowledging the receipt and consideration of the cited references, by returning the two Information Disclosure Citations, properly initialed for each of the cited references.

Conclusion

The Office is respectfully requested to consider each of the references cited both in the enclosed Information Disclosure Statement and in the August 26, 2002 Information Disclosure Statement, and to return an initialed copy of the two forms PTO-1449 with the next communication concerning this application.

Allowance of Claims 1-13, and 38-41 at an early date is respectfully requested.

Respectfully submitted,



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Appendix -- "Marked-up" Version of Amendment to Claim 1

1. (once amended) A method for assaying angiogenesis *ex vivo*, said method comprising the steps of:

(a) embedding a three-dimensional mammalian tissue sample in a matrix, wherein the tissue sample has at least one cut surface exposing blood vessels; wherein the three-dimensional tissue sample comprises multiple layers of cells comprising blood vessels and other cells of the tissue; and wherein the architecture of the tissue sample, including blood vessels, supportive stromal elements, neural cells, and endothelial cells, is substantially intact and has not been disrupted as compared to that of comparable tissue *in vivo*; and wherein the three-dimensional tissue sample does not consist of an isolated artery or an isolated vein;

(b) supplying to the embedded tissue sample a medium that supports the growth of the tissue sample;

(c) incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels, if any, to grow into the matrix surrounding the tissue sample; and

(d) observing or measuring the angiogenic vessels, if any, that grow into the matrix surrounding the tissue sample.